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Review

Telomere shortening during aging: Attenuation by antioxidants and anti-inflammatory agents

Kedar N. Prasad[a], Meixia Wu[b], Stephen C. Bondy[c,*]

[a] Engage Global, San Rafael, CA 94903, United States
[b] Acacia Home Health, Fountain Valley, CA 92708, United States
[c] Center for Occupational and Environmental Health, Department of Medicine, University of California, Irvine, CA 92697-1830, United States

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ABSTRACT

Telomeres are a repeated sequence -of bases found at the ends of chromosomes. In humans, this sequence is TTAGGG, which is repeated over 2000 times. Telomeres protect the ends chromosomes from fusion with nearby chromosomes, and allow effective replication of DNA. Each time a cell divides, 25–200 base pairs are lost from the terminal sequence of chromosomes. By becoming truncated during cell division, telomeres protect essential genes from being shortened and thus inactivated. In addition, telomeres are sensitive to inflammation and oxidative stress, which can further promote telomere shortening. Reduction in the length of telomeres leads to the cessation of cell division and thus cellular senescence and apoptosis. This review discusses evidence for the role of oxidative stress and inflammation in regulating the length of telomeres in mammalian cells during senescence. Evidence is presented suggesting that antioxidants and anti-inflammatories can reduce the pace of shortening of telomere length during aging. The distinctive properties of transformed cells suggest that treatment with such materials will have a deleterious rather than a protective effect on such abnormal cells.

1. Introduction

Ageing can be defined as a gradual deterioration of organ function toward the end of the life span. Environmental-, dietary-, lifestyle-related factors, and heritable gene mutation can all contribute to the individual rate of aging. Levels of oxidative stress, inflammation, mitochondrial dysfunction, antioxidants, shortening of telomeres and gene mutations are all likely to play a role in determining the pace of cellular aging. There is considerable evidence to show that reduction in the length of telomeres is associated with failure of cell division and senescence of normal cells, and that oxidative stress and inflammation can contribute to the rate of attrition of telomere length. These studies are discussed in this manuscript together with some suggestions as to how aging events may be beneficially influenced by exogenous factors.

Telomeres consist of a repetitive sequences of TTAGGG located at the end of chromosome needed for the replication of DNA. Telomerase reverse transcriptase (TRT) is the catalytic subunit of telomerase enzyme that is responsible for maintaining telomere length by adding telomere repeats TTAGGG at the end. On the other hand, telomeric repeat-binding factor-2 (TRF-2) is needed for the telomere maintenance, cell cycle progression, and protection of the ends to avoid chromosomal fusion (Hanaoka et al., 2005; Kim et al., 2009).

One of the widely held hypotheses is that aging of mammalian cells is due to shortening of telomere length (Mikhelson and Gamaley, 2012). This is supported by the fact that point mutations within the telomere cause accelerated attrition of telomere length and also lead to premature aging (Fyhrquist and Saijonmaa, 2012). There is substantial evidence to show that increased oxidative stress and inflammation play a central role in shortening the length of telomeres possibly by decreasing the activity of telomerase and/or TRF-2 level.

The length of telomeres is maintained in cancer cells despite increased oxidative stress and inflammation (Ennour-Idrissi et al., 2016; Bertorelle et al., 2014; Rode et al., 2016). Telomerase is expressed in over 95% of cancer types, at a much higher levels than in normal adult tissues. This is due to the reactivation of the gene hTERT, which is generally silent in adult tissues, leading to production of telomerase reverse transcriptase, TERT (Bermudez et al., 2007), and reappearance of active telomerase ribonucleoprotein. Inhibition of oxidative stress protects telomerase activity in normal cells but inhibits that in tumor cells. This apparent contradiction has been accounted for by the higher redox homeostasis threshold that exists in cancer cells causing them to have a high demand for reactive oxygen species (ROS), (Li et al., 2016a).

This review discusses the role of oxidative stress and inflammation

* Corresponding author.
E-mail address: scbondy@uci.edu (S.C. Bondy).

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in regulating the length of telomeres in mammalian cells. In addition, it presents evidence to show that antioxidant and anti-inflammatory agents may reduce the pace aging by curtailing the rate of shortening of telomere length. It should be emphasized that, in view of the large overlap between oxidant and inflammatory events the distinction between protective agents acting on either, is rather arbitrary.

2. Effects of oxidative stress on telomere length

Evidence from a variety of human studies that show oxidative status and telomere length are closely related. These studies are enumerated here.

2.1. Clinical reports

Several clinical reports illustrate the link between pro-oxidant events and telomere status.

2.1.1. Periodontitis

Increased oxidative stress and inflammation is associated with reduced leukocyte telomere length in patients with periodontitis (Masi et al., 2011).

2.1.2. Parkinson's disease

Enhanced oxidative stress is found in patients with Parkinson's disease and that shortened length of telomeres in the blood cells is associated with this disease (Watfa et al., 2011).

2.1.3. Depression

Gene expression of oxidative defense enzymes superoxide dismutases (SOD1 and SOD2), catalase (CAT) and glutathione peroxidase (GPX1) were significantly lower in oligodendrocytes derived post-mortem from patients suffering from major depressive disorders. This was accompanied by a reduction of both telomeric length and levels of TERT in oligodendrocytes but not astrocytes (Szebeni et al., 2014).

2.1.4. Diabetes

Increased oxidative stress together with shortened length of leukocyte telomeres is found in type 1 and type 2 diabetes. In addition, older people with central obesity, hyperglycemia, insulin resistance and lower antioxidant levels had shorter leukocyte telomere length (Ma et al., 2013). The monocyte telomere shortening observed in type 2 diabetes could be due to increased oxidative DNA damage to monocyte precursors during cell division (Sampson et al., 2006).

2.1.5. Aging

Elderly men living in Greece have lower indices of oxidative stress and higher antioxidant levels, than a corresponding population of elderly Dutch men, living in a more stressful urban setting and a diet less rich in antioxidant nutrients. The length of telomeres in leukocytes was significantly greater in the Greek relative to the Dutch population (De Vos-Houben et al., 2012). This suggests causal relationship between increased oxidative stress and shortening of the telomere length during aging.

2.1.6. Twin study

In a metabolomics study of over 300 adult twins, there was a relation between indices of oxidative stress, decline in organ function and reduced leukocyte telomere length (Zierer et al., 2016). While this does not imply causality, such a correlation supports findings from studies involving more defined studies using in vitro systems

2.1.7. Dyskeratosis congenita

Dyskeratosis congenita (DC) is a multi-system disorder characterized by defects of the skin, nails, and mucous membrane. Most cases are also associated with bone marrow dysfunction. This disease exhibits severe telomere abnormalities attributable to defects in six genes coding for those proteins, such as TERC and TERT responsible for maintaining telomere length (Kirwan and Dokal, 2009).

2.2. Isolated systems

Findings directly paralleling the human studies described above have also been obtained in isolated cell systems. Some examples:

Increased oxidative stress induced by treatment with H2O2 shortened the length of telomeres isolated in mouse skeletal muscle fibers (Ludlow et al., 2014).

Enhanced oxidative stress induced by treatment with *tert*-butyl hydroperoxide or L-buthionine-(S, R)-sulphoximine shortened the length of telomeres and caused senescence in human endothelial cells (Kurz et al., 2004).

Mild hyperoxia reduced the length of telomeres and induced senescence in human fibroblasts (von Zglinicki et al., 1995).

While it is clear that oxidative events can lead to telomere shortening, it is not fully established whether this is due to inhibition of TERT and/or TRF2. Additional studies on effects of ROS donors on telomere length in normal cell models as well as animal models of aging are needed to identify the mechanisms underlying such events.

2.3. Immune system

The cells of the immune system are very sensitive to shortening of telomere length, since the competency of immune system depends upon cell renewal and clonal expansion of T-and B-lymphocytes. These cells can increase the activity of telomerase and thereby limit telomere attrition in cells undergoing active proliferation. Oxidative stress is one of the factors that induce senescence in immune cells (Kaszubowska, 2008). In many cell types from patients with coronary heart disease (leukocytes, CD34+ peripheral blood stem cells and progenitor cells, monocytes, granulocytes, B-lymphocytes, and CD4+ T lymphocytes), the length of telomeres was shorter than in their age-matched control subjects. Shortening of telomere length was the most pronounced in cytotoxic CD8 T lymphocytes (Spyridopoulos et al., 2009). The same study reported that cytomegalovirus infection in CD8+CD28 (−) T cells caused further shortening of telomere length. T cell senescence occurs prematurely in patients with rheumatoid arthritis. The low levels of the DNA double-strand break repair nuclease MRE11A caused damage to telomeres and induced senescence in rheumatoid arthritis t-lymphocytes. Inhibition of the activity of MRE11A in healthy T cells induced senescence, whereas overexpression of MRE11A in T cells from patients with rheumatoid arthritis reversed these cells to normal phenotypes (Li et al., 2016b). Thus the length of telomeres in T cells depends upon the activity of MRE11A. In the CD3+T-cells from patients with myelodysplastic syndrome (MDS), the high rate of attrition of telomere length occurs because of lower telomerase activity as well as reduced expression of telomere reverse transcriptase mRNA (Yang et al., 2013).

3. Effects of inflammation on telomere length

Some examples of the intimate relation between inflammatory events and telomeric length are listed:

3.1. Obesity

Obesity is associated with enhanced oxidative stress and inflammation (Hulsegge et al., 2016; Zhao et al., 2016). Weight gain during adulthood and obesity contribute to shorter leukocyte telomere length in adults younger than 60 years of age (Muezzinler et al., 2016). Higher Body Mass Index (BMI) and obesity at the age of 25 can lead to a reduced length of leukocyte telomeres (Wulaningsih et al., 2016).

3.2. Caloric restriction

A causal relationship between metabolic signs of inflammation and telomere shortening is suggested by the finding that caloric restriction prevented decline in leukocyte telomere length, whereas a high intake of omega-6 fatty acids with pro-inflammatory activity increased the rate of loss of length of leukocyte telomeres (Kark et al., 2012). Caloric restriction also improves cardiac function in diabetic mice and this is accompanied by increased telomerase activity (Makino et al., 2015).

Another study reported that pro-inflammatory diet causes accelerated rate of attrition of leukocyte telomere length compared to that found with anti-inflammatory diet (Garcia-Calzon et al., 2015b).

3.3. Inflammation

Increased serum homocysteine levels together with elevated inflammation has been found to be associated with reduced length of leukocyte telomeres in adults 55 years or older (Shin and Baik, 2016). Populations of the elderly (85–99 years of age), and centenarians (100–104 years old), maintained long telomeres and low levels of basal inflammation. The offspring of centenarians expressed similarly long telomeres and reduced basal inflammatory activity relative to age matched controls (Arai et al., 2015). However, low levels of inflammation were found to be better predictors of healthy aging than telomere length (Arai et al., 2015). In a separate study, supercentenarians (105–109 years old) were found to have significant shorter leukocyte telomeres than centenarians (100–104 years old), suggesting progressive attrition of telomeres after the age of 104 years (Tedone et al., 2014). Hyperactivity of the transcriptional factor NF-kB and enhanced expression of pro-inflammatory cytokines, such as TNF-alpha, IL-6, and IFN-gamma in circulating macrophages, contribute to the shortening of telomeres and the onset of senescence (Zhang et al., 2016).

3.4. Reciprocity of inflammation and telomerase

Mutations in human telomerase RNA component (TERC) and telomerase reverse transcriptase (TERT) increased the levels of pro-inflammatory cytokines in the lung and caused premature aging in alveolar stem cells (Chen et al., 2015). These results are important in that they indicate that the relationship between impaired telomeres and inflammation may be reciprocal. Thus, aging may involve interplay of inflammatory events and telomeric dysfunction.

3.5. Mechanisms of action of oxidative stress and inflammation on telomere length

The mechanisms of oxidative stress-induced shortening of the length of telomere are not fully understood. Oxidative stress can impair endonuclease III-like protein 1 (Nth1) protein responsible for the repair oxidative DNA damage leading to the loss of telomere length (Vallabhaneni et al., 2013). Oxidative stress causes a decline in the ability of DNA to repair oxidative damage that results in shortening of telomeres during aging (Duan et al., 2005). Deficiency of the nucleotide excision repair pathway renders cells more sensitive to oxidative stress causing increased telomere attrition (Ting et al., 2010). Oxidative stress increases the expression of phosphorylated cyclin-dependent kinase inhibitor p16 (INK4a) and this induces senescence in endothelial progenitor cells (EPCs) associated with shortening of telomere length (Yang et al., 2008). Increased oxidative stress may enhance the expression of miR-195 that inhibits SIRT1 leading to senescence associated with shortening of telomeres (Kondo et al., 2016). Increased oxidative stress as well as pro-inflammatory cytokines, also upregulate the expression of miR-146a (Jiao et al., 2015; Pogue et al., 2011). Increased expression of miR-146 was found in senescent human umbilical vein endothelial cells (HUVECs) (Olivieri et al., 2013). Taken together, these studies suggest that oxidative stress and inflammation may shorten telomere length by upregulating the expression of miR-146.

4. Influence of antioxidants on telomere length

Several reports indicate that antioxidants can reduce the velocity of telomeric shortening:

4.1. Carotenoids

In a study of over 3000 US adults, increased serum levels of carotenoids were significantly associated with longer leukocyte telomeres. It was suggested that high intake of carotenoid-rich food may play a role in protecting telomeres against oxidative damage (Min and Min, 2016).

4.2. Cardiac disease

Using endothelial cells (EC) isolated from arterial segments of patients with severe coronary artery disease, treatment with *n*-acetylcysteine (NAC) reduced the rate of shortening of telomeres, but did not significantly delayed the onset of senescence (Voghel et al., 2008). In contrast, normal endothelial cells in culture show gradual senescence together with increased production of ROS and mitochondrial dysfunction. In addition, telomerase reverse transcription (TERT) is translocated from the nucleus to the cytoplasm leading to Src-kinase activation. Treatment of these cells with NAC prevented these changes and delayed senescence (Haendeler et al., 2004). Endothelial cells from heart disease patients are already damaged; and may respond to NAC differently from the normal endothelial cells.

4.3. Diet

Diet seems to be a significant factor in determining telomere status. Several human clinical reports exist suggesting the beneficial effects of antioxidants in the diet, on telomere function. Mechanistic understanding of events underlying these reports, is complicated by the simultaneous presence of more than one anti-oxidant. However, such a multiplicity of compounds reflects a more typical condition and may provide benefits due to unanticipated synergies.

In children and adolescents, longer telomere length in leukocytes has been related to a diet rich in antioxidants, while diets rich in white bread were associated with shorter telomeres (Garcia-Calzon et al., 2015a).

In men and women, ages 40–85, supplementation with omega-3 fatty acids, thereby decreasing the ratio of dietary omega-6:omega-3 fatty acids, reduced oxidative stress, and increased the length of telomeres (Kiecolt-Glaser et al., 2013). Since omega-6 fatty acids exhibit pro-inflammatory activity, whereas omega-3 fatty acids show anti-inflammatory activity, decreasing this ratio would decrease the proportion of pro-inflammatory cytokines and thus reduce the rate of attrition of telomere length. A diet rich in monounsaturated fatty acids such as in the olive oil of the Mediterranean diet, can retard leukocyte telomere length attrition, (Gomez-Delgado et al., 2016).

In healthy Japanese adults, elevated levels of beta-carotene and alpha tocopherol protected buccal mucosal cell from telomere shortening (Yabuta et al., 2016). In an Australian stroke prevention study population (average age 66 years), enhanced plasma concentrations of lutein, zeaxanthin, and vitamin C were associated with longer leukocyte telomeres (Sen et al., 2014).

A human population aged 35–55, received dietary supplementation with a commercial preparation of multivitamins containing omega-3-fatty acid, carotenoids, coenzyme Q10, selenium, vitamin D and alpha-tocopherol for 12 weeks, increased the activity of lymphocytic telomerase without affecting the length of telomeres (Balcerczyk et al., 2014). This report found that antioxidant treatment improved several anti-

aging indices without changing the length of lymphocyte telomeres. These results might suggest that shortening the length of telomeres may not be associated with aging. However, some observations in this study are conflicting. For example, that antioxidant treatment increased the activity telomerase without affecting the length of telomeres that appears to be inconsistent. It may be that the improvement of several indices of aging without changing telomere length may be a reflection of complex multi-factorial nature of the aging process.

4.4. Antioxidant treatment in isolated cells, or animals

Many studies using animal models or isolated cell lines corroborate the human reports described above. Some examples:

Heart/muscle-specific manganese superoxide SOD-deficient mice (H/M-SOD2 -/) are characterized by dilation of the end-diastolic dimension, inhibition of telomerase activity, reduction of the levels of TERT, and telomere repeat-binding factor-2 (TRF-2) proteins. Administration of EUK-8, a superoxide dismutase (SOD) and catalase mimetic in SOD-deficient mice prevented tall of these changes in the heart tissue (Makino et al., 2011).

Reduced length of telomere and activity of telomerase together with evidence of DNA damage were found in human diploid fibroblasts after repeated cell passages. Treatment of fibroblasts with tocotrienol-rich fraction prevented senescence by restoring telomere length and telomerase activity (Makpol et al., 2011).

Vitamin E suppressed endogenous telomerase activity in ovarian cancer cells, but has no effects on telomerase-negative normal ovarian surface epithelial cells (Bermudez et al., 2007). This is another example, repeatedly described in this review, of the opposite effect of antioxidant or anti-inflammatory agents, on atypical cells as opposed to normal cells.

5. Influence of anti-inflammatory agents on telomeres

In a manner analogous to the properties of anti-oxidants, several agents whose qualities include anti-inflammatory properties, appear able to influence telomerase activity and hTERT expression:

5.1. Resveratrol

There are numerous reports of the ability of resveratrol to contribute toward the maintenance of telomere length. Orally administered resveratrol fed to old mice can reverse age related changes in ovarian telomerase activity, telomere length and age-related gene expression, resulting in the profile of these parameters to resemble those of young mice rather than control untreated old animals (Liu et al., 2013). In an isolated culture system, resveratrol can enhance telomerase activity of endothelial progenitor cells and thereby delay their senescence (Wang et al., 2011). This in vitro effect suggests that resveratrol can act directly on cells rather than its abilities being mediated by systemic changes. Resveratrol is known to enhance levels of anti-inflammatory microRNAs, while repressing pro-inflammatory microRNAs (Latruffe et al., 2015). Thus the mechanism of protection of telomeres may in part be mediated by microRNAs.

5.2. Curcuminoids

Curcuminoids are also able to enhance telomerase activity assayed by telomere repeat amplification protocol (TRAP), in a cell free system, (Taka et al., 2014). This implies a direct effect on telomerase not involving the immune system. An interesting paradox, reflecting that found in the case of anti-oxidants involves the responses of malignant cells to curcumin. In T47D cells a breast cancer line, curcumin exerted cytotoxic effects and inhibited telomerase gene expression (Nasiri et al., 2013). Another example of this paradoxical effect of curcumin on transformed cells, is the report that curcumin inhibits telomerase and down-regulates hTERT mRNA in glioblastoma and medulloblastoma cells (Khaw et al., 2013).

5.3. Aspirin

Aspirin is the archetype of anti-inflammatory drugs and has also been found to stimulate telomerase activity in normal bone marrow mesenchymal stem cells leading to improvement in their immunomodulatory capacity (Chen et al., 2014). Once again, the effect of aspirin on malignant cell lines is the opposite of responses elicited from normal cells. The telomerase activity in several cell types isolated from colon carcinoma, is inhibited (He et al., 2006). Since this occurs together with reduced levels of hTERT mRNA, a direct effect on gene expression is indicated. Aspirin, also inhibits the telomerase activity of a non-malignant but pathological cell type. This is the polymorphonuclear neutrophil derived from carotid plaques (Li et al., 2013). Thus it seems that any cells with sufficiently abnormal metabolism respond to anti-inflammatory agents in a manner opposite to that of normal cells.

5.4. Catechins

Another class of compounds expressing the same ambivalence toward cells of malignant origin in contrast to normal cells, are the catechin polyphenols found in green tea. This class of compound prevents shortening of telomere length and cardiac myopathy in manganese superoxide dismutase deficient mice (Oyama et al., 2017), but inhibits TERT expression in human breast cancer cells (Meeran et al., 2011). Similarly, in a transformed cell line, both mRNA of hTERT and telomerase were decreased after treatment with epigallocatechin gallate (Wang and Lei, 2015). Cardiac hypertrophy initiated by a pressure overload leads to loss of TRF-2, and progressive loss of telomeres and apoptosis in rat heart myocardium. Treatment of rats with epigallocatechin, the major component of green tea, and quercetin prevented such changes (Sheng et al., 2013).

5.5. Statins

Other drugs whose properties contain a significant anti-inflammatory component, are the statins. Several reports of their ability to promote telomerase activity exist, including human trials (Janić et al., 2016). It has been proposed that the chronic inflammation associated with aging and many disorders, plays a role in facilitating telomere shortening and that statins can ameliorate this (Kordinas et al., 2016). Since inflammation involves increases in oxidative events, these process are obviously closely linked and it has been proposed that anti-aging effects of statins involve inhibition of telomere shortening by either direct or indirect reduction of oxidative damage to telomeric DNA (Olivieri et al., 2012).

5.6. Stress

Exposure to psychosocial stress has been associated with increased oxidative stress and inflammation (Maes et al., 2011; Maes, 2013; Wilson et al., 2013). Children exposed to stressful life events had shorter leukocyte telomeres upon reaching middle-age (Osler et al., 2016). Adults exposed to psychosocial stress have similarly reduced length of leukocyte telomeres (van Ockenburg et al., 2015). However, there are also conflicting reports in this area. Telomerase activity in stressed rats was elevated by 54% (Beery et al., 2012). The effect of stress on increasing levels of telomerase has been replicated in a human trial involving exposing both dementia patients and their caregivers to acute psychological stress (Epel et al., 2010). Since stress elevates levels of cortisol and this results in depressed immune function, this suggests that inflammatory activity can translate into telomere shortening. It seems that the telomeric response to stress is biphasic. Beneficial at the levels of a transient healthy challenge, but harmful if excessively

prolonged when factors other than cortisol levels may come into play.

6. Conclusion

Overall, these studies from isolated systems and human populations all point to a causal link between inflammation and oxidative stress as determinants of telomere integrity. How the processes underlying such links occur and how the microRNAs interact with these events, are all not well understood and more investigations on effects of pro-inflammatory cytokines on telomere length in normal cell models as well as animal models of aging are needed to support the idea that aging involves interplay between inflammation and telomeric dysfunction. The studies discussed in this review suggest the possibility of therapeutic interventions to retard cellular aging and thereby reduce the incidence of age-associated diseases. Since transformed or otherwise abnormal cell types appear to respond to anti-oxidants and anti-inflammatory agents in a manner opposite to normal tissues, consumption of these exogenous materials seems to exclusively benefit cells of non-pathological origin. While the reasons underlying this major difference are not well understood, the application of dietary micronutrients one of the safest approaches toward optimal aging and increased longevity. This could include anti-oxidant and anti-inflammatory agents including targeted dietary modifications or scientifically designed mixtures (Prasad and Bondy, 2014).

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